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Immunotherapy, the next step in the treatment of myeloma

The improved understanding of the molecular pathways involved in cancer development has allowed for the rational design of drugs that target and selectively interfere with oncogenic signaling pathways, thus moving from the “one size fits all” approach to a more personalized therapy. As a consequence, cancers, including multiple myeloma, are now treated effectively, with prolonged survival.¹ Nevertheless, nearly all myeloma patients will experience acquired resistance arising from a number of alterations, such as gene mutation, amplification or alternative splicing, and different mechanisms may be in operation in different cells due to intra-tumor heterogeneity. In addition, the tumor and its microenvironment may lead to immunosuppression in the bone marrow,² causing a loss of tumor immunosurveillance and providing protection to targeted cell death.³ In this scenario, recent findings suggest the central role of immunotherapeutic agents, including monoclonal antibodies, with a dual mechanism of action, as they can act directly against cancer cells and regulate cellular immune response.⁴

This is indeed the model of action of elotuzumab. Elotuzumab is a humanized monoclonal antibody targeted against Signalling Lymphocytic Activation Molecule Family member 7 (SLAMF7). It has a novel dual mechanism of action, as it binds to SLAMF7 on myeloma cells, while also binding to CD16 on natural killer (NK) cells, activating NK cells to lyse the antibody-bound tumor cells, thus with selective killing of myeloma cells and minimal effects on normal tissue. In addition, elotuzumab directly activates NK cells by binding to SLAMF7 on their surface and improves their antimyeloma activity through the interaction with signaling intermediary EAT-2.⁵ Based on this knowledge, elotuzumab is under evaluation in clinical trials and it showed to be safe and effective as single agents, as well as in combination with other agents such as bortezomib and lenalidomide.⁴

In the *Lancet Haematology*, the authors present final results from a phase 1b/2 randomized study of elotuzumab – 10 mg/kg or 20 mg/kg - in combination with lenalidomide and dexamethasone in relapsed myeloma patients who received one to three prior lines of therapy.⁶ Twenty-nine patients were enrolled in the phase 1 and 73 in the phase 2. In the latter, 36 patients were randomized to receive elotuzumab at 10 mg/kg and 37 patients to elotuzumab at 20 mg/kg. The overall response rate was 84%, including a very good partial response rate of 42%, and the median progression-free survival was 28.6 months. No significant differences in outcome were detected between elotuzumab at 10 or 20 mg/kg. Although cross trial comparisons should be considered with caution, the efficacy

of this combination was also confirmed in the phase 3 ELOQUENT-2 trial,⁷ where patients receiving elotuzumab plus lenalidomide-dexamethasone had a relative reduction of 30% in the risk of disease progression or death compared with the control group. Of note, in the subgroup of patients receiving elotuzumab and who achieved a very good partial response or better the median progression-free survival was not reached. Thus, elotuzumab plus lenalidomide-dexamethasone showed to be particularly effective with reduced tumor mass.

The phase 1b-2 study showed that the elotuzumab combination was well tolerated, and the most common, all grade adverse events were diarrhea (66%), muscle spasms (62%) and fatigue (56%). The good safety profile was confirmed in the phase 3 ELOQUENT-2 study,⁷ which found no significant difference between elotuzumab-lenalidomide-dexamethasone and the control group in terms of rates of grade 3-4 toxicities: neutropenia was 34% versus 44%, thrombocytopenia 19% versus 20%, and anemia 19% versus 21%, in the elotuzumab and in the control groups, respectively. Elotuzumab induced an increase in lymphocytopenia (77% versus 49%), which may reflect alterations in lymphocyte trafficking, including NK cells, with no evidence of autoimmunity or other sequelae of immune dysregulation.

The results of the phase 1b-2 study, and in particular those of the ELOQUENT-2 study, suggest that the combination of elotuzumab plus lenalidomide-dexamethasone can be considered one of the new standards of care for relapsed/refractory myeloma patients, with no additional toxicity. Longer follow-up is needed to assess whether a subgroup of patients may have a very prolonged remission duration. Further evidence is needed to support the role of treatment strategies that combine cytoreduction and tumor immunosurveillance in multiple myeloma, as already demonstrated in other tumors.

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